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VASCULAR COMPLICATIONS OF DIABETES MELLITUS*

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VASCULAR disease is by far the most serious complication of clinical diabetes mellitus. Atherosclerosis of the medium-sized arteries, according to Warren and LeCompte,[1] is the largest single cause of death among diabetic persons. The most alarming feature is the high incidence of serious vascular degeneration in relatively young people who have had diabetes for a long time. Coronary thrombosis is the cause of death in diabetics less than 40 years of age ten times as frequently as in nondiabetics of the same age.[2] Patients in this age group who have had diabetes mellitus for more than 20 years almost never escape the development of intercapillary glomerulosclerosis.

Clinical and Pathologic Manifestations

The most important clinical effects are caused by involvement of the coronary and the cerebral arteries, the arteries of the legs, the arterioles of the kidneys, and the capillaries of the glomeruli and the retinas. The atherosclerotic lesion is characterized by focal thickening of the intima with the deposition first of lipid and later of calcium. Renal arteriosclerosis associated with chronic glomerulonephritis and hypertension is much more frequent and severe in patients with long-standing diabetes, particularly young patients.

Intercapillary glomerulosclerosis is the name used originally by Kimmelstiel and Wilson to describe the hyaline masses between the glomerular tufts in diabetes. They formerly were thought to originate between the capillaries. Recently, Bergstrand and Bucht,[3] using the electron microscope, have demonstrated that

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the early lesions are in the capillary basement membrane and in the basement membrane of Bowman's capsule. The disease may be either diffuse or nodular. In the diffuse form the thickening extends rather evenly along the course of the glomerular capillaries. In the nodular form there are masses of clear, acellular material deposited between the capillary tufts. The diffuse form is seen fairly commonly in glomerulonephritis and in old age. The nodular form, on the other hand, particularly when severe, is almost exclusively a change typically associated with diabetes.

The exact nature of the material forming the nodules is not known. When stained by hematoxylin and eosin, it looks like hyalin, but the fact that it takes a periodic acid—Schiff reagent suggests a content of carbohydrate, perhaps of mucopolysaccharide.[4] Many such nodules also accept stains for lipids. Muirhead, Montgomery, and Booth[5] recognize two types of lesions: one is due to a collection of collagen-like material in the capillary wall, and the other is due to an intercapillary collection of fibrinoid-like substance. It seems likely from the work of Lynch and Raphael[6] that the accumulated material arises from erythrocytes.

Lonergan and Robbins[7] report that among 62 autopsies of patients with hemochromatosis and diabetes, no intercapillary glomerulosclerosis was found. Twenty-one of the group had diabetes for five years or longer, and in three it existed for more than 15 years. In patients having diabetes only, approximately 15 per cent would be expected to have the lesions of intercapillary glomerulosclerosis. Estimates of the frequency of the disease vary greatly, probably because of differences in criteria used. Laipply, Eitzen, and Dutra[8] estimated from autopsy material an incidence of 64 per cent.

The usual progress of the disease appears to be slow;[9] it is associated with arteriosclerosis, and frequently with pyelonephritis. In the early stages the condition may be suspected because of albuminuria, but not until it is moderately advanced can an assured diagnosis be made without renal biopsy or autopsy. It causes about 30 per cent of the total number of deaths of young diabetic patients who have had the disease for more than 15 years.[10,11]

The clinical manifestations of the disease include diabetes of long duration, albuminuria, edema of the legs, arterial hypertension, and anemia. Diabetic retinopathy is an almost invariable accompaniment. The serum albumin content is less than normal, and generally there are an increased amount of beta-globulin and concentrations of cholesterol and lipoprotein in the blood. There are doubly refractile bodies in the urine. In the terminal phase there may be a great reduction in insulin requirement. It frequently is difficult to decide how much of this is a feature of the disease or the result of the inevitable low food intake of an ill patient.

Diabetic retinopathy is a degenerative disease also of the capillaries. Its frequency has greatly increased in the past 20 years because of the longer duration of the diabetes as compared to its frequently short course formerly. The first manifestation

of the disease is the appearance of minute, circumscribed, saccular dilatations of the capillaries, said to be chiefly on the venous side of the capillary beds. These formerly were called punctate hemorrhages, and it may be difficult to distinguish between the two types of lesions, especially since small true hemorrhages may be contiguous with the dilatations. The walls of the capillaries in some sections appear to be thin and in others to be thickened from the deposition of a hyaline material. The veins are irregularly dilated and tortuous. Minute or massive hemorrhages arise from the capillaries and veins. Yellowish-white, so-called "hard" exudates appear, and eventually extensive formation of new vessels may result in retinal detachment.

Microaneurysms are not exclusively associated with diabetes; they occur with hypertension, glaucoma, and with occlusion of the central retinal vein. Although, according to pathologic studies,[12,13] retinopathy invariably occurs in patients with intercapillary glomerulosclerosis, only 58 per cent of diabetic patients with retinopathy had intercapillary glomerulosclerosis.

The course of the disease varies greatly. It may cause blindness within a few months or it may remain relatively inactive for years; it is only in the unusual instance that temporary improvement occurs. Fagerberg[14-17] connects neuropathy closely with vascular disease. In a study of biopsy specimens of nerves in 150 cases of diabetic neuropathy he has shown that this lesion may be largely vascular in origin. The specific lesion appears to be one of ischemic degeneration of the myelin sheath, the vasae nervorum being occluded with polysaccharide deposits. It is easy for me to accept the idea that vascular disease often is a factor in diabetic neuropathy, but it is difficult to understand how a lesion of this type could be solely responsible for the most common diabetic neuropathy that disappears completely and permanently within a few days or a few weeks during good diabetic control—the neuropathy commonly accepted in the past to be "metabolic."

Factors Influencing the Frequency and Severity of Vascular Lesions

Duration of diabetes is the most important single factor in the etiopathogenesis of vascular degeneration. This correlation has been demonstrated strikingly by White and Waskow[4]: among 200 patients in whom diabetes developed before the age of 15 years and who survived more than 20 years with the disease, nephropathy was present in 50 per cent, calcified arteries in 75 per cent, and retinal hemorrhages in 80 per cent. Paul and Presley[18] found retinopathy in 45 per cent of patients who had juvenile diabetes of 15 or more years' duration. Others[19-21] reported vascular degeneration in long-standing diabetes to vary from 60 to 83 per cent of patients. Complications seldom occur before the tenth year of the disease, but are almost always present after the twentieth year.

The difference between the frequency both of coronary occlusion and of nephropathy in diabetic persons as compared with that in normal persons is much more notable in those less than 40 years of age than it is in elderly persons.

Bell[22] in a report based on 1,559 necropsies on diabetic subjects observed that nephropathy was present in all less than 40 years of age who had had the disease for 20 years; whereas, in persons who died at the age of 60 years or older who had had the disease for 20 years, the incidence fell to about 40 per cent.

The prognosis is not altogether unfavorable. Although vascular lesions almost always are present in persons who have had diabetes for a long time, they are not always severe. Bell's[22] necropsy findings indicate that 30 per cent of 93 patients who lived more than 20 years with diabetes did not have serious vascular disease.

Severity of the disease and its control. Most clinicians who treat diabetes extensively believe that there is a relationship between both the severity and the degree of control of diabetes to vascular degeneration, but there is not complete unanimity concerning either factor. Both severity and degree of control are difficult, if not impossible, to define accurately. The severity of the disease cannot be measured well on the basis of insulin requirements. I agree with Ricketts[23] that "The true test of severity is the behavior of the disease when insulin is withheld." In many young diabetics taking no more than 30 units of insulin per day, acidosis develops promptly when insulin is omitted; it is chiefly in this group that vascular disease occurs with the greatest frequency and severity. Yet, there are some young diabetics who by any criteria have severe diabetes, who will escape vascular disease for more than 25 years; and other young adults who have been almost aglycosuric and have had normal blood sugar values for years and have not required insulin, in whom retinopathy develops. The fact that mild or potential diabetes may be associated intimately with vascular disease was demonstrated by Bartels and Rullo,[24] who showed that in glucose tolerance tests of 100 unselected patients with peripheral vascular disease, there were 59 for whom the glucose tolerance curve was abnormally high.

There is even sharper disagreement about the importance of good control of diabetes in the prevention of vascular disease. Wagener, Dry, and Wilder[25] presented data on 200 patients seen frequently during periods as long as 25 years. Not one escaped retinopathy, regardless of the age at onset or the severity of the diabetes or the type of treatment used. On the other hand, Root, Pote, and Frehner[26] reported that in 451 patients with diabetes of from 10 to 34 years' duration, nephropathy occurred in less than 2 per cent of those with good control, while 67 per cent of those with poor control had moderate or severe retinopathy. It is just as important and much more difficult to explain why one fourth of the patients with good control had severe retinopathy and one third of the patients with poor control had none. We recently studied 101 patients who have had diabetes for 15 years or longer. Twenty-two of these patients have had their disease for more than 25 years; five (23 per cent) had no evidence of degenerative disease, and seven (32 per cent) had no evidence of retinopathy in dilated pupils observed by one of our consultants in ophthalmology.

Mucopolysaccharides. Because mucopolysaccharides are deposited in excess in

the affected tissues in both the nephropathy and the retinopathy of diabetes, investigators have examined the possible relationship of glucose, glucosamine, and carbohydrate bound to alpha-2-globulin in the blood. There has been little to suggest that high concentration of blood sugar is harmful in itself, but some evidence indicates that great fluctuations may be harmful. Góth, Lengyel, Nádasdi, and Sávely,[27] by using glucose and insulin in rats to cause notable fluctuations in blood sugar content, produced renal lesions that simulated intercapillary glomerulosclerosis. It has been clinically demonstrated that blood content of protein-bound mucopolysaccharides is higher in the presence of evident vascular disease than in its absence.[28] Lerman, Pogell, and Lieb[29] observed an increase in alpha-2-globulin in patients with retinopathy, but the values were identical in patients without retinopathy and in normal persons tested. The serum glucosamine content was high in diabetic patients with or without retinopathy. Because it is known that the concentration of serum mucopolysaccharides is increased in conditions characterized by destruction of tissue, it is suspected that the increase in these substances may be the result, and not the cause, of vascular damage. Neilsen and Poulsen,[30] however, found increased concentrations of similar substances in the blood of diabetic patients without complications as well as in those with renal disease.

Serum cholesterol and lipoproteins. Much has been written in recent years about the relationship of elevated concentrations of cholesterol and lipoprotein in the blood in atherosclerosis in diabetic patients, and in those without diabetes. A causal relationship has been implied or claimed, but none has been proved to exist; also there is no proof that high concentrations of blood lipids are the cause of diabetic retinopathy or nephropathy.

Pomeranze and Kunkel[31] studied 273 diabetic patients. Total blood lipid contents were above normal average in half of the patients, and below in the other half. Barach and Lowy[32] studied 614 diabetic patients and found the blood cholesterol concentration elevated in 58 per cent, and normal in 42 per cent. These authors found blood lipoprotein values elevated in less than half of their diabetic patients; others[33] have found no significant differences between these values in diabetic patients and in normal persons.

In general, it appears that the lipoprotein and cholesterol values tend to be elevated in poorly controlled diabetes more frequently than in the well controlled. In diabetic patients who have renal disease, the blood lipoprotein values almost always are elevated, probably caused by the renal lesions and not the cause of them. In retinopathy without measurable renal disease the lipoprotein concentration usually is normal.

Pituitary and adrenal influence. Since Poulsen[34] published the record of a patient in whom diabetic retinopathy disappeared over a period of years after Sheehan's syndrome due to pituitary failure developed, considerable interest has been aroused as to the relationship of pituitary and adrenal factors as to cause or aggravation

of diabetic vascular disease. Treatment with ACTH has been reported to cause microaneurysms as well as renal lesions similar to the intercapillary glomerulosclerotic type in alloxan diabetic rabbits,[35] and glomerulosclerosis associated with an increase in alpha-2-globulin has followed treatment with cortisone under similar circumstances.[29]

Such laboratory findings are not readily correlated with clinical data. Most diabetic patients do not have any signs suggestive of Cushing's disease; furthermore, most patients with acromegaly or Cushing's syndrome, even those with diabetes, do not have retinopathy. However, in most of these patients, diabetes has not been known to exist for 15 years. In our own experience with 22 acromegalic patients with diabetes, four had retinopathy. Diabetes had been known to exist no longer than eight years. Of 21 patients with diabetes and Cushing's syndrome, two had retinopathy after diabetes of eight or nine years' duration. It seems likely, therefore, that underlying factors that are a part of diabetes, or intimately connected with it, are the chief causes of such lesions, and that pituitary-adrenal hyperactivity may under some circumstances be an aggravating factor. One of our patients with acromegaly and diabetes of four years' duration died and autopsy was performed. Proliferative retinitis was present and yet there was no evidence of intercapillary glomerulosclerosis. In another similar instance[36] in which proteinuria also was present, retinopathy was observed but there also were no signs of intercapillary glomerulosclerosis.

Heredity. Although there is little in the way of factual data available to implicate heredity as a cause of vascular degeneration, this possibility is gaining consideration. It is clear that when the diabetes is mild and the vascular disease is severe, or where in contrast the diabetes is severe and the vascular disease is absent, other factors must be at work. Such factors may be constitutional and perhaps hereditary.

Treatment

The cause of vascular degeneration associated with diabetes is incompletely understood. Vascular degeneration appears to be an almost integral part of the disease, although in general, the more severe or poorly controlled the disorder, the greater is the component of vascular degeneration. If this is true, then it must follow that until diabetes is prevented, diabetic vascular damage will occur. Because prevention is not foreseeable in the near future, our aims must be: (1) reduction of the incidence by combating those factors known to be associated with the development of diabetes, (2) early detection of vascular involvement, and (3) as complete control of the diabetes as is possible. It is believed, although it remains to be proved, that detection and treatment of diabetes mellitus early in its course prevent complications. One of the best tests for early detection is the postprandial blood sugar test. It can be performed by physicians as part of the standard procedure of the initial examination of all patients. Special attention

must be given to patients with strong family histories of diabetes, and especially to obese patients.

If it is worthwhile to detect diabetes early, it is logical that it should be treated and controlled with meticulous care. The best possible diabetic control should be applied to all patients. The blood cholesterol content should be maintained at normal if possible. If this does not follow control of sugar in the blood and the urine by ordinary means, a low-fat diet may be prescribed; if that is unsuccessful, a diet in which unsaturated fats are allowed, so that the total daily intake of fat is from 60 to 90 gm., may be effective.

Vitamins in excess of normal requirements, hesperidin and rutin have not been proved to be of value in preventing or reversing retinopathy or nephropathy.

It is important to avoid all urinary infections, and for their detection urine cultures are useful. For men, mid-voided specimens may be used, and for women, clean voided specimens can be obtained with meticulous attention to cleanliness, thereby avoiding the risk of introducing harmful bacteria by catheter. The use of properly selected antibiotics will control most lesions of pyelonephritis.

For retinopathy, radiation therapy to the pituitary and to the eyes has proved to be of little or no value.

Hypophysectomy is drastic, and there have been few if any unequivocally and permanently beneficial results. For the amelioration or reversal of diabetic retinal and renal lesions the operation has been performed in a total of about 30 patients reported in the studies of Luft and Olivecrona,[37] and Kinsell, Lawrence, Balch, and Weyland[38]; in seven patients adrenalectomy was done.[39] The results have not been strikingly favorable. The paradox here seems to be in the facts that pituitary-adrenal hyperactivity was not known to be present before surgery, and that in addition these patients required postoperative support indefinitely with hydrocortisone or cortisone—the very substances supposedly pathogenically responsible.

In the uremia of intercapillary glomerulosclerosis, a low-sodium diet and diuretics will control most of the edema, and a high caloric intake will spare the body's protein. In extreme renal failure, a daily protein intake of less than 40 gm. may be necessary to reduce azotemia. Transfusions of packed erythrocytes, sodium-free albumin, or dialysis are measures of limited value and only to be used under extreme circumstances.

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MANAGEMENT OF THE DONOR SITE

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EVERY surgeon who cuts a skin graft must face the problem of how to manage the donor site. However, since it is traditional among surgeons to assume that the area of primary treatment, be it on the surface of the body or within the chest or abdomen, is the important consideration in a surgical procedure; the incidental surface lesion, be it the suture line or the donor site of a skin graft, has been relegated to a position of insignificance. This is particularly true of the donor site, which, so far as the patient is concerned, may be the most painful, disabling, and cosmetically deforming portion of the surgical procedure. It behooves us, therefore, if we are to deal with skin grafts, to make every effort to manage the donor site in such a way as to minimize both the discomfort to the patient and the residual scar.

Mechanism of Donor Site Regeneration

In taking a thin split-skin graft, it is often assumed that enough surface epithelium is left in islets on the dermis to provide foci of regeneration which enlarge and ultimately fuse. Since it is practically impossible to cut a graft of such thinness, in actual practice this method of repair probably does not take place. It can be seen microscopically that all of the epithelial elements within the dermis having direct connection with the raw donor site act as such epithelial islets. The hair follicles are most prominent in this process, with sebaceous glands and sweat glands being of less importance. This regenerative process usually has started by the second day following the taking of a graft, and is complete by the fifth or sixth day. Keratinization and proliferation of the new epithelial layer proceed rapidly to produce a normal-appearing microscopic skin picture by the tenth day *(Figs. 1-4)*. These observations as to time, pertain specifically to the clean, uninfected donor site from which a thin split-skin graft has been taken.

Converse and Robb-Smith[1] noted that the quality of donor-site repair is directly proportional to the rapidity of its healing, which in turn depends primarily on the thickness of the graft; e.g., after thin split-skin graft removal, the healing period is 6 to 10 days; after thick split-skin graft removal the healing period may approach two months.

Until recently, the almost universal method of handling the donor site has

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been to use a firm, occlusive dressing over some kind of gauze. This dressing is designed to produce complete immobilization of the raw donor site and the immediately overlying gauze to reduce oozing and loss of serum by its pressure, and by excluding the outside world to maintain a reasonable degree of sterility and thus to avoid infection.Furthermore, it has been assumed that this method offers the best chance for rapid healing. In actual practice the results from the use of this type of occlusive dressing have left much to be desired. First, many of the available donor sites used most frequently, such as the posterior thigh, the buttocks, the abdominal wall, and the back are difficult to immobilize, even by the unusually ingenious operator. Inadequate immobilization that allows slipping of the gauze layer over the raw donor site, virtually assures breakdown of the normal healing process. Secondly, whereas the use of pressure for from 24 to 36 hours on the new donor site may be useful in reducing fluid loss, there is no evidence that it has any significant value thereafter. Thirdly, while a closed dressing may be of value in controlling bacterial contamination in the first few hours after the taking of a skin graft, it is doubtful that this is of much importance in terms of ultimate healing.

Although every plastic surgeon has his own particular method of managing the donor site, there has been little discussion of this problem in the surgical literature. In general, the concept of the "occlusive dressing" has been accepted.[2] The differences in technic have been related largely to the types of ointment and gauze that are placed next to the raw surface. Dry, fine-mesh cotton and nylon gauzes have been used without any ointment, and in recent years some surgeons have advocated the use of a perforated sheet of Cellophane-like material known as "Teflon" to prevent adherence of the dressing to the donor site. A plastic spray to provide a firm, but thin dressing has been tried in an attempt to improve the occlusive dressing. This has been generally unsatisfactory. Of the materials mentioned, the most widely and successfully used has been fine-mesh gauze, lightly coated with Vaseline, covered by a resilient pressure dressing.

In recent years a number of surgeons have managed donor sites by the exposure method, such as that used in the treatment of burns. Although this method has been fairly satisfactory, it has had the same deficiencies that characterize its use for burns. These are specifically the problem of drainage and oozing in the first 24 to 72 hours, and the tendency of the thick coagulum to crack, with subsequent superficial infection. Except for these deficiencies, the serum coagulum, once it has formed, provides an almost perfect dressing material; it is strongly attached to the raw surface, it has moderate flexibility, it is not tender, it is surprisingly tough, and it has little bulk.

Artz, Bronwell, and Sako[3] in 1955 reported a modification of the open technic, adding a layer of gauze to the coagulum, thus making use of the coagulum to protect the donor site, and at the same time minimizing the difficulties inherent in the use

of complete exposure of the wound. We have been using this type of donor-site dressing since 1952. The following data present our experience over a seven-year period.

Fig. 1. Cross section of typical medium-thickness split-skin graft; magnification x 40.

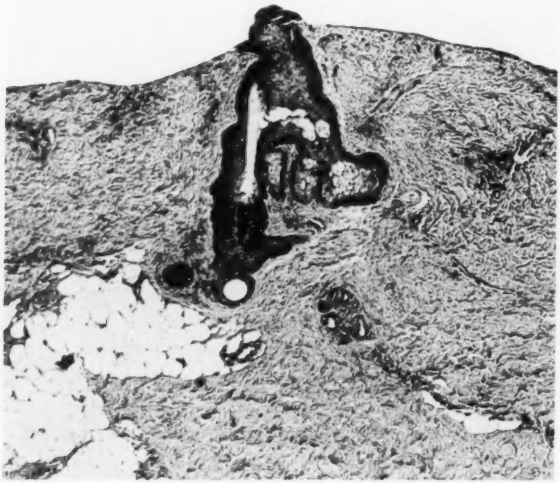

Fig. 2. Section of donor site three days after removal of graft, showing early proliferation of hair follicle epithelium; magnification x 40.

Fig. 3. Section of donor site five days after removal of graft; the proliferating epithelium has started to cover the raw connective-tissue surface; magnification x 40.

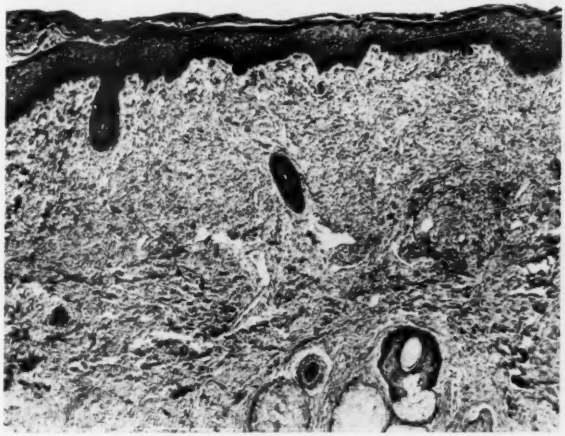

Fig. 4. Section of donor site six days after removal of graft; epithelial resurfacing is complete; magnification x 40.

Technic

Immediately after the cutting of the skin graft, a single layer of almost dry fine-mesh Vaseline gauze is applied to the donor site. An occlusive dressing of the usual type is applied with moderate pressure, to control initial oozing and to protect the donor site in the immediately postoperative period. In from 12 to 24 hours, the occlusive portion is removed, leaving only the single layer of greased gauze attached to the raw surface. This is accomplished without difficulty, but with some discomfort to the patient. The donor site is kept exposed to air, and within another 24-hour period has developed a thin, pliable coagulum, of which the fine-mesh gauze has become an integral part. The gauze provides a structural framework for the clotting process, and prevents subsequent cracking of the coagulum. During this second 24-hour period there may be minimal oozing from the gauze surface, which can be gently removed with a gauze sponge, without injury to the underlying raw area. The coagulum rapidly becomes firm, and by the end of the third day is immune to the usual trauma of bed activity and early ambulation *(Figs. 5 and 6)*.

The edges of the coagulum, which gradually loosen as healing takes place, are kept trimmed. The coagulum is allowed to separate spontaneously, without manual assistance; this eliminates the tearing of newly formed epithelium, which occurs so frequently when the usual gauze dressing is removed. This process may

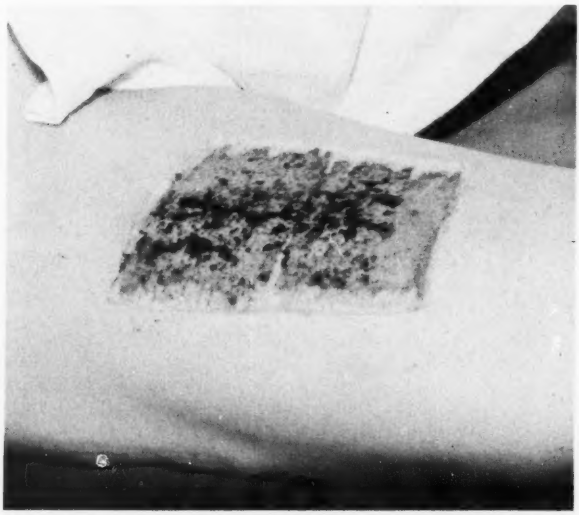

Fig. 5. Usual thigh donor site with gauze-serum coagulum intact two days after removal of outside dressing.

be completed within a week, or may require several weeks for its completion, depending on the thickness of the original graft.

Results

It is of no statistical value to report the exact number of complications experienced by the authors when using the standard occlusive dressing prior to their using the above-described method. Such a figure carries little significance without accurate analysis of such variables as thickness of graft, location of the donor site, extent of immobilization of the area, and probably most important, the continually changing resident personnel entrusted with the dressing and management of the donor site. Furthermore, it is difficult to decide just what constitutes a reportable donor-site complication. However, in an effort to provide a reasonable base line for evaluation, it can be stated that of 100 donor sites managed with the usual occlusive dressing, more than 30 per cent became wet and superficially infected to such a degree that more than "Band-Aid" care was required.

In the past seven years, approximately 1,400 donor sites have been managed by this gauze-coagulum method. There has been no instance in which the entire donor site has become wet, even in the uncooperative patient, and the over-all incidence of complications requiring treatment is less than 5 per cent. This figure is most significant when we consider that at least one third of the donor sites were high on the posterior aspect of the thigh, on the buttock, or on the back.

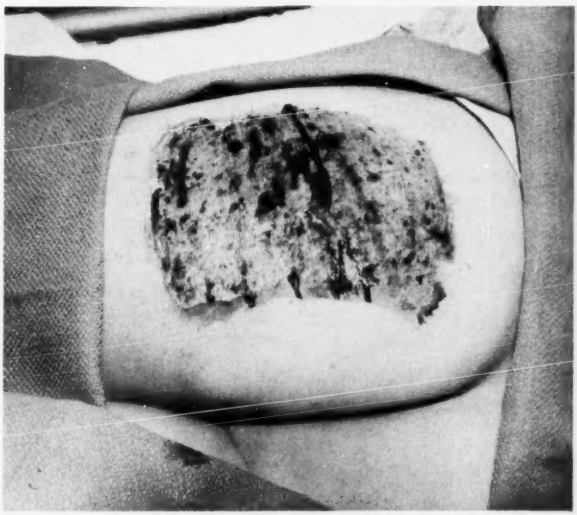

Fig. 6. Buttock donor site easily managed by modified exposure method.

In general, healing of the donor site has not been slowed by the elimination of the pressure dressing. Pain to the patient has been reduced significantly, particularly that secondary to surface infection. Consequently, the surgeon's problems have been comparably lessened.

Summary

A method of donor-site dressing has been discussed. This utilizes an occlusive dressing over fine-mesh Vaseline gauze for the first 12 to 24 hours. At that time the occlusive portion is removed and the fine-mesh gauze alone is left in place to become an integral part of the covering coagulum. The results using this method have been superior to those obtained with the standard occlusive dressing.

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POSTDIALYTIC CHANGES IN SERUM OSMOLARITY AND IN BLOOD UREA OF 23 PATIENTS

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and
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PATIENTS in chronic renal failure, and to a lesser extent those in acute renal failure, may have a relative decrease in urinary output after treatment with the artificial kidney. It has been suggested that the cause of this postdialytic "oliguria" may be due to a decrease in osmotic load. We know of no study that substantiates or refutes this thesis, and therefore undertook to investigate a possible correlation between postdialytic changes in urinary output and in osmolarity of serum.

Methods and Material

Twenty-three patients in different stages of acute and chronic renal failure were treated with twin-coil disposable artificial kidneys for a total of 64 dialyses. Before and after each dialysis, samples of blood were taken for standard laboratory tests and to determine the osmolarity of the serum. For control purposes, 24 samples of blood were taken from normal blood donors for determinations of osmolarity of the serum. Determinations of concentrations of sodium, chloride, bicarbonate, and urea in the serum, and of hematocrit readings were performed in our hospital laboratory under the supervision of John W. King, M.D., Ph.D., and Willard R. Faulkner, Ph.D.

Osmolarity of serum was determined with the Fiske osmometer, which operates on the physical principle that both the osmotic pressure of a solution and the depression of the freezing point of the solvent are directly proportional to the molecular concentration of the dissolved substance (the total ion and molecular counts in the case of ionized solutions). The osmometer measures the depression of the freezing point, but is calibrated to read in units of osmotic pressure directly in milliosmols per liter. Prior to every determination, the osmometer was standardized with a solution of 300 m-osM. of sodium chloride per liter in water.

Results

After dialysis, with few exceptions, there was a change toward normal of the individual values for osmolarity, sodium, chloride, and bicarbonate in the serum, and in the hematocrit readings. The 64 dialyses are classified into four groups

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according to the changes in serum osmolarity after treatment: Group A—serum osmolarity increased in a range of slightly above 0 to 18 m-osM.; Group B—it decreased in a range of slightly less than 0 to -10 m-osM.; Group C—it decreased in a range of -10 to -20 m-osM.; and Group D—it decreased more than 20 m-osM.

Figure 1 is a graph of the changes in serum osmolarity before and after the dialyses. It is evident that the greatest decreases occurred in those patients who had extremely high osmolarities prior to dialysis. During the day of, and on the day after dialysis, decreases in average urinary output occurred in every group. The magnitudes of the decreases were not correlative with changes in osmolarity. Invariably, on the second day after dialysis, urinary output had attained the predialytic volume.

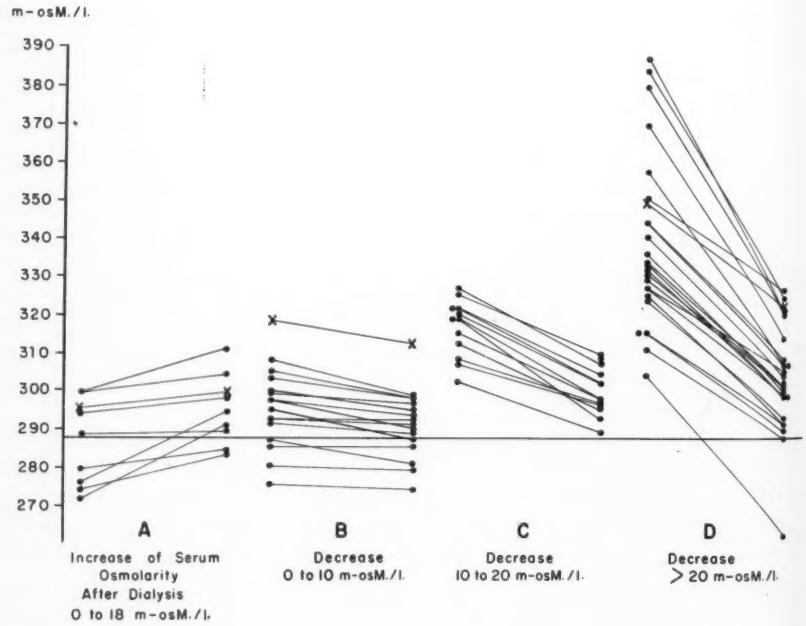

Fig. 1. Graph showing changes in serum osmolarity before and after 64 dialyses (the horizontal line represents the average normal serum osmolarity). In the three cases indicated by X at the beginning and X at the end, urea was added to the dialyzing (bath) fluid.

If the decrease in osmolarity of serum is effected mainly by a decrease in blood urea, then a graph of the values would define a straight line; we obtained such a general, but crude, correlation *(Fig. 2)*. A number of cases fall outside the

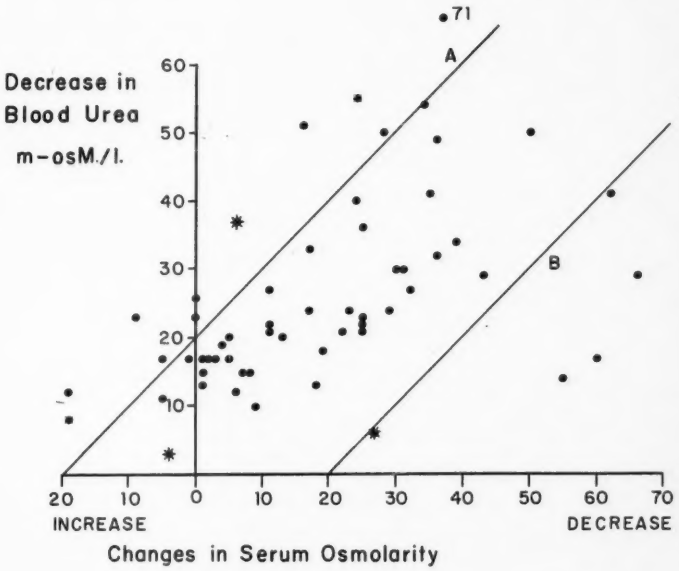

Fig. 2. Graph showing decreases in blood urea and changes in serum osmolarity. There is a crude correlation between change in blood urea and change in osmolarity. The points above line A and below line B are discussed in *Figures 3* and *4*. The three cases in which urea was added to the bath are indicated by asterisks.

limiting lines of A and B, indicating that in these cases there is no correlation between serum osmolarity and the change in blood urea. The points above line A represent a decrease in blood urea but only a relatively small decrease in serum osmolarity. When in these cases the decrease in blood urea was plotted against the combined increase of the concentrations of serum sodium, serum chloride, and serum bicarbonate, it was evident indeed that a large increase in this sum had occurred up to 40 mEq. per liter *(Fig. 3)*. Similarly, a relatively small reduction in blood urea associated with a large decrease in serum osmolarity (points under B in *Fig. 2*) may be explained by a decrease in the sum of the concentrations of sodium, chloride, and bicarbonate in the serum; decreases in the sums were as much as 28 mEq. per liter *(Fig. 4)*. One case did not conform to this relationship.

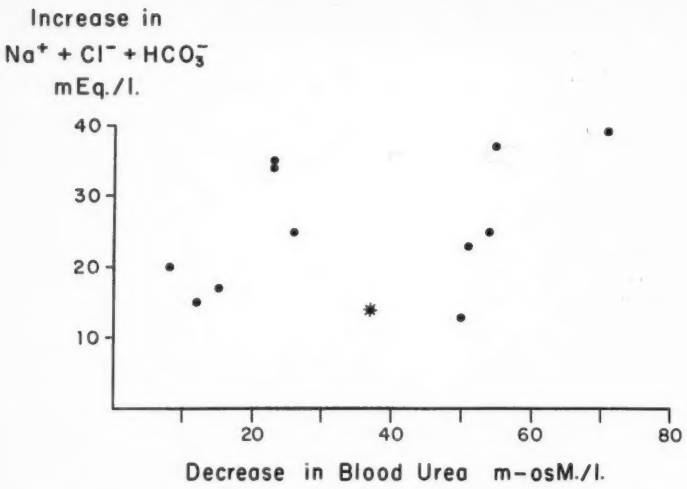

Fig. 3. Graph showing increases in the sums of serum sodium, chloride, and bicarbonate in the cases in which there were large decreases in blood urea but relatively small decreases in serum osmolarity. The asterisk indicates that urea was added to the bath.

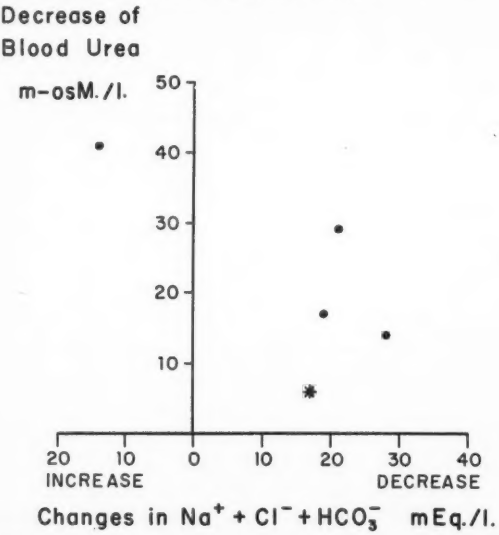

Fig. 4. Graph showing decreases in the sums of serum sodium, chloride, and bicarbonate in four cases in which there were relatively small decreases in blood urea with large decreases in serum osmolarity. The asterisk indicates that urea was added to the bath.

Summary

Osmolarity of serum was determined in samples of blood from 23 patients before and after 64 dialyses. Dialysis may result in large, small, or minimal decreases in serum osmolarity, and even an increase. Most frequently there was a decrease in serum osmolarity, generally correlative with a decrease in blood urea. Discrepancies in the correlation between decrease in serum osmolarity and decrease in blood urea can usually be explained by increases in the sums of serum sodium, serum chloride, and serum bicarbonate concentrations in the opposite direction.

ANATOMIC ANOMALIES COMMON TO MYELOMENINGOCELE OF INFANCY AND SYRINGOMYELIA OF ADULTHOOD SUGGEST A COMMON ORIGIN

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Department of Neurological Surgery

THE fact that an infant with myelomeningocele may have a syrinx in association with the Arnold-Chiari malformation,[1, 2] together with the fact that this same association occurs in the adult with syringomyelia[3-6] led to a search of the literature for other anatomic anomalies shared by the infant with myelomeningocele and the adult with syringomyelia. This search revealed that each may have hydrocephalus, hydromyelia (dilatation of the central canal), syringomyelia (syrinx or cavity paralleling the central canal), Arnold-Chiari malformation, Dandy-Walker malformation, membranes enclosing the foramens of the fourth ventricle, glial heterotopia, and skeletal anomalies—scoliosis, hemivertebra, fused vertebrae, anomalous ribs, deformity of the feet, enlargement of the skull and of the vertebral canal.

Hydrocephalus

In most cases of myelomeningocele there is increased intracranial pressure and progressive dilatation of the ventricles, indicating an uncompensated hydrocephalus. This hydrocephalus may be of the communicating or of the noncommunicating variety.[7] It is not widely known that syringomyelia in the adult may be accompanied by dilated ventricles but with normal intracranial pressure, i.e., compensated hydrocephalus. Netsky[8] found dilatation of the ventricles in three of four cases of syringomyelia in which the brain was examined at necropsy *(Fig. 1)*. Encephalography likewise will show that the ventricles frequently are dilated in patients with syringomyelia and that they may or may not communicate with the subarachnoid space.[3-5] Thus, we find that hydrocephalus occurs both in the infant with myelomeningocele, and in the adult with syringomyelia, and that it may be communicating or noncommunicating. The conditions differ in that the hydrocephalus in the infant usually is severe and uncompensated, whereas in the adult it is mild and compensated.

Hydromyelia and Syringomyelia

In 1876, Leyden[9] stated his belief that syringomyelia in the adult is a "rest" of a congenital hydromyelia that "cuts itself off" from the central canal. Recently Greenfield[10] also has pointed out that there is a link between hydromyelia and syringomyelia, and stated that cases are apt to be assigned to one or the other category according to whether or not the cavitation has produced the typical

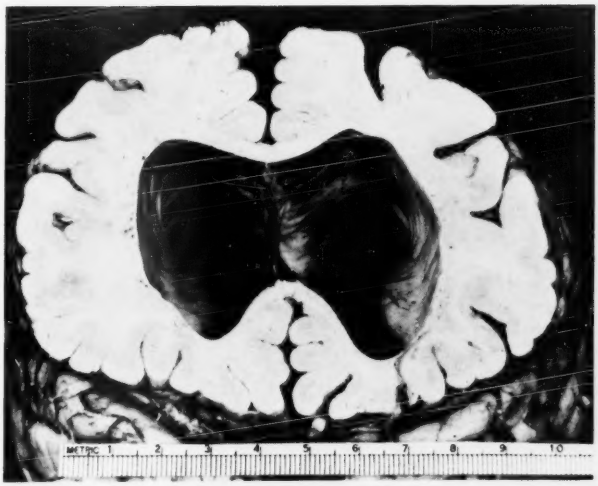


Fig. 1. Hydrocephalus in a woman of 47 years with symptomatic syringomyelia for 15 years. The cord was cystic from its junction with the medulla to its sacral portion. (Courtesy of Netsky, M.G.: A.M.A. Arch. Neurol. & Psychiat. 70: 741-777, Dec. 1953.)

symptoms of syringomyelia during life. Netsky[8] among others has shown that syringomyelia in the adult may constitute merely a diverticulum of a hydromyelia so that both conditions coexist.

The infant with myelomeningocele usually has hydromyelia *(Fig. 2)*,[2,10-12] and in addition may have a true syrinx. Lichtenstein[1] described a case in which a syrinx communicated with the central canal of the cord near its juncture with the fourth ventricle *(Fig. 3)*. In a 26-week-old infant with myelomeningocele, Cameron[2] observed a syrinx that extended from the level of the sixth cervical vertebra to the third thoracic vertebra and measured 0.4 cm. in maximum diameter. At its upper end only it communicated with the hydromyelic central canal. Therefore, the infant with myelomeningocele, as well as the adult with clinical syringomyelia, may have hydromyelia and a communicating syrinx.

Because the ventricles and the central canal constitute a single cavity, the term "hydrocephalomyelia" has been proposed[3] to describe the state in which both are dilated.

Arnold-Chiari Malformation

Chiari,[13] in 1891, gave a complete description of three types of deformity of the hindbrain caused by hydrocephalus of the forebrain. Despite the fact that this antedated Arnold's[14] inadequate description of the deformity, his pupils Schwalbe

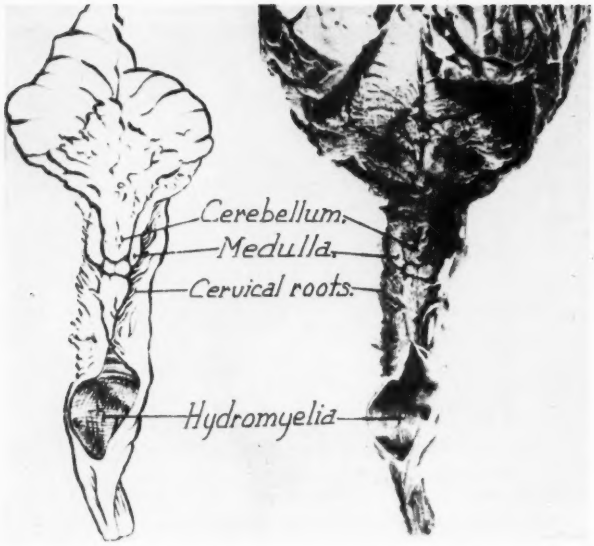


Fig. 2. Hydromyelia in an infant with myelomeningocele. (Courtesy of D'Errico, A.: South. M. J. 35: 247-252, March 1942.)

and Gredig[15] subsequently entitled Chiari's type 2 the "Arnold-Chiari malformation." In his more commonly quoted second paper, Chiari[16] described 14 cases of his type-1 deformity, all in adults or in adolescents, only one of whom had myelomeningocele. He also described seven cases of his type-2 deformity, all in infants with myelomeningocele. In type 1 the herniation included the cerebellar tonsils, but not the fourth ventricle, a deformity now frequently referred to as "pressure coning." In type 2 the more pronounced herniation included the vermis and the fourth ventricle as well, with an associated posterior bulging of the medulla, and because of the accompanying caudal dislocation of the upper cervical cord, the emerging nerve roots pursued a cephalad course to their points of exit. Chiari believed that type 2 was merely a severe form of type 1, and that both were caused by hydrocephalus of the forebrain. He found hydromyelia in both types.*

In 17 instances of the "Arnold-Chiari malformation" in adolescents and adults described by Gardner and Goodall,[3] none were associated with myelomeningocele. There was a syringomyelic type of sensory loss in 12 patients, and a cystic cervical cord was demonstrated at operation in 10 of these 12 as well as in three others who did not present the clinical picture of syringomyelia. These 17 hindbrain malformations resembled Chiari's type 1, in that the cerebellar hernia consisted of

**Chiari's type 3 consisted of a herniation of the hindbrain through the bony defect of a cervical spina bifida.*

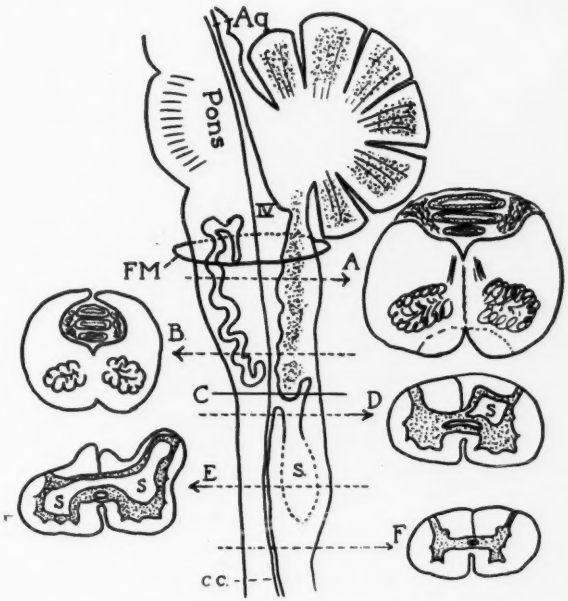


Fig. 3. Schematic drawing of a midsagittal section through the hindbrain and upper cervical cord of an infant with hydrocephalus, Arnold-Chiari malformation, and myelomeningocele. FM indicates the foramen magnum, S the syrinx, c.c. the central canal, and C the level of transection at necropsy. Note the absence of the foramen of Magendie. (Courtesy of Lichtenstein, B. W.: Arch. Neurol. & Psychiat. 49: 881-894, June 1943; A.M.A. Arch. Neurol. & Psychiat.)

the tonsils, but in some there was herniation of the fourth ventricle as well, a feature that Chiari included under his type 2 *(Fig. 4)*.

Thus we see that the Chiari type-1 malformation in the adult with syringomyelia may have some of the features of Chiari's type-2 deformity of infancy. Conversely, the infant born with a mild myelomeningocele may exhibit Chiari's type-1 deformity, as was illustrated by Chiari's[16] own experience mentioned above, and also by case 19 of Russell.[17] Therefore, although the Chiari malformation present in the adult with syringomyelia usually is type 1 and that in the infant with myelomeningocele usually is type 2, nevertheless, transitional forms do occur both in the adult and in the infant. This intermingling of the features of the two types lends support to Chiari's conviction that type 2 is merely a severe form of type 1.

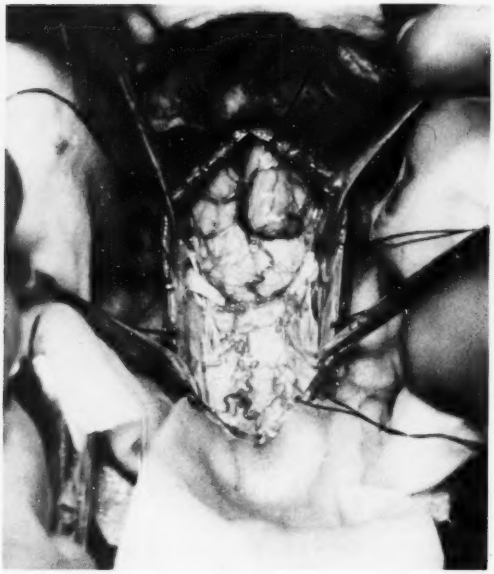


Fig. 4. Herniation of the cerebellar tonsils, posterior bulging of the medulla, and upward-slanting cervical nerve roots in a patient with syringomyelia. This represents a transitional form between Chiari's type-1 and type-2 malformations. (Courtesy of Gardner, W. J.; Abdullah, A. F., and McCormack, L. J.: J. Neurosurg. 14: 591-607, Nov. 1957.)

Dandy-Walker Malformation

It is not generally recognized that an infant with myelomeningocele may prove to have an enormous dilatation of the fourth ventricle instead of the anticipated Arnold-Chiari malformation *(Fig. 5)*. Dandy[18] showed a photograph of such a patient, and Benda[19] also described this association. In Benda's patient, the fourth ventricle formed a huge sac that, together with a separation of the cerebellar hemispheres, constituted his "Dandy-Walker syndrome." Examination of the spinal cord of this infant "revealed myelomeningocele and congenital syringomyelia of the hydromyelic type . . ."

When encountered in the adult, the Dandy-Walker malformation is mild and may be accompanied by the typical clinical picture and operative findings of syringomyelia as described by Gardner, Abdullah, and McCormack.[4] Thus, the Dandy-Walker malformation has been encountered both in the infant with myelomeningocele and in the adult with clinical syringomyelia.

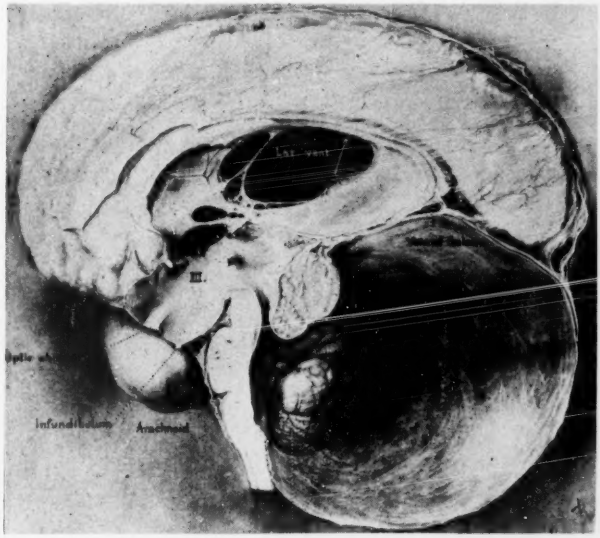


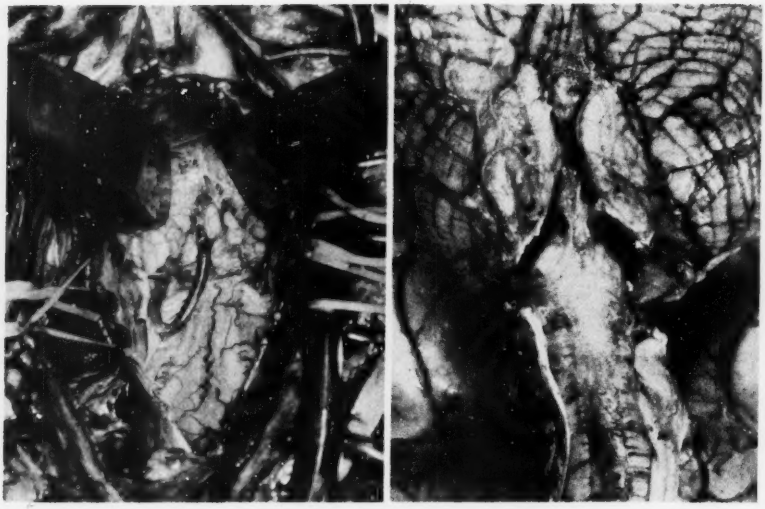
Fig. 5. Sagittal section through the brain of an infant with hydrocephalus due to congenital occlusion of the foramens of Luschka and Magendie. The enormously dilated fourth ventricle constitutes Benda's[19] "Dandy-Walker Syndrome." (Courtesy of Surg. Gynec. & Obst.: Dandy, W. E.: Surg. Gynec. & Obst. 32: 112-124, Feb. 1921.)

Membranes Enclosing the Foramens of the Fourth Ventricle

Membranes enclosing the distended foramens of a dilated fourth ventricle are the diagnostic feature of the Dandy-Walker malformation whether encountered in the infant with myelomeningocele or in the adult with syringomyelia. The attachments and the microscopic appearance of these membranes indicate that they represent persisting portions of the embryonic rhombic roof.[20] It is not generally known that similar membranes may enclose these foramens in the Arnold-Chiari malformation as well, both in the infant with myelomeningocele and in the adult with syringomyelia. When present in the Chiari type-1 deformity, either in an adult (case 3 of Gardner, Abdullah, and McCormack[4]) or in an infant (case 19 of Russell[17]) the membranes are readily demonstrable *(Fig. 6, A and B)*. In the Chiari type-2 malformation, the foramens of Luschka are concealed in the herniated mass compressed within the spinal canal. A sagittal section in some cases, however, will clearly show a membrane enclosing the foramen of Magendie *(Fig. 7)*.

Glial Heterotopia

Most authors in discussing myelomeningocele have described an associated glial heterotopia. Cooper and Kernohan[21] found extruded heterotopic glial nests



A B

Fig. 6. A, Membrane obstructing the foramen of Magendie in a Chiari type-1 malformation in an adult with syringomyelia. B, Similar finding in an infant with a Chiari type-1 malformation, a lumbosacral meningocele, and a tethered cord. Each foramen of Luschka also was closed by a bulging membrane in this case. (Courtesy of Russell, D. S.: M. Res. Council Special Rep. Ser. No. 265; H. M. Stationery Office, 1949, 138 pp.; the Controller, H. M. Stationery Office, 1959.)

in the meninges in a series of 50 necropsies, in 34 of which there were associated congenital anomalies of the nervous system, the most common ones being: spina bifida, hydrocephalus, syringomyelia, and hydromyelia. Gardner, Abdullah, and McCormack[4] described foci of glial heterotopia in the leptomeninges of the pons, the medulla, and the spinal cord of an adult with syringomyelia. Glial heterotopia, therefore, is another anatomic anomaly that is present in the infant with myelomeningocele and in the adult with syringomyelia.

Skeletal Anomalies

In association with syringomyelia, skeletal anomalies such as scoliosis, hemivertebra, fused vertebrae and cervical ribs have been described. Gardner and Goodall[3] found scoliosis in eight of 17 patients, fused vertebrae in two patients, and hemivertebra in one patient. Similar but more severe skeletal anomalies are found in infants with myelomeningocele. Cameron,[2] in 26 such infants, found kyphoscoliosis in nine, sometimes associated with multiple hemivertebrae; and there were absent, deformed or supernumerary ribs in four patients. Fused vertebrae are difficult to recognize in infants, because ossification is incomplete, but Ingraham and Scott[11] found fusion associated with myelomeningocele, as did Feller

Fig. 7. Membrane obstructing the foramen of Magendie in an infant with myelomeningocele and Chiari type-2 malformation. (Compare the attachment of the membrane at the obex to that in *Figure 5.*) (Courtesy of Moncrieff, A., and Norman, A. P.: Greenfield, J. G.: *Neuropathology:* Edward Arnold (Publishers) Ltd., 1958, 640 pp.)

and Sternberg.[22] Clubfoot is encountered frequently in the infant; whereas, in the adult with syringomyelia, pes cavus is a common finding.

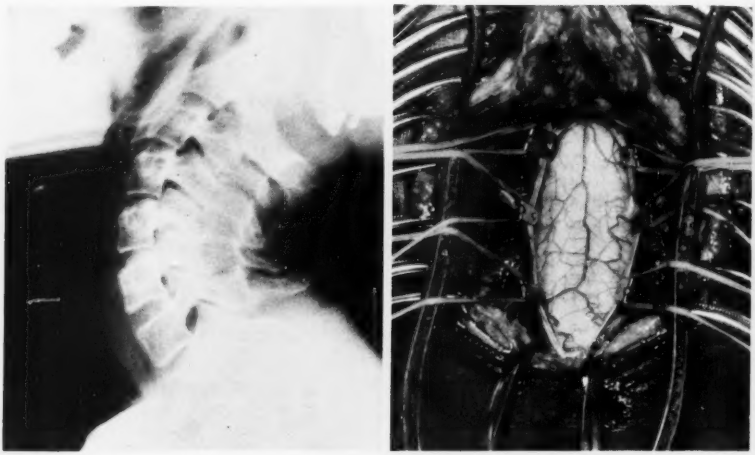
Expansion of the Cranio-Vertebral Axis

In the infant with myelomeningocele the cranial vault usually is enlarged. The same may be true of the adult with syringomyelia, although the enlargement is less frequently observed and less severe. Netsky[8] described a patient with syringomyelia who had a large brachycephalic skull and evidence, on roentgenograms, of long-standing internal hydrocephalus. Gardner, Abdullah, and McCormack[4] also found this in one of their patients.

Dilatation of the lumbar canal at the level of the spina bifida is always present in infants with myelomeningocele. There may be an associated dilatation of the cervical portion of the canal as was described by Feller and Sternberg[22] in their case of lumbar myelomeningocele mentioned above.

I have observed dilatation of the cervical portion of the vertebral canal in a 16-year-old boy with syringomyelia, and also in an 11-year-old girl *(Fig. 8, A and*

B). This increased size of the lumen of the bony spine and skull obviously is not due to a primary defect in osteogenesis, but represents an expansion secondary to increased intraluminal pressure.



A B

Fig. 8. A, Dilatation of the vertebral canal of an 11-year-old girl with syringomyelia. B, Same case at operation; a syrinx always is distended in this fashion in the living subject as compared to its usual collapsed state at necropsy. The distention of the cervical cord in this case appears to have been responsible for the dilatation of the vertebral canal just as the distention of the ventricles in congenital hydrocephalus is responsible for the enlargement of the cranial vault.

Discussion

The neural tube of the embryo is a closed cavity consisting of the primitive ventricles and the central canal of the cord. Its lumen is extremely large compared to the thickness of its walls, thus constituting physiologic hydrocephalus and hydromyelia, or hydrocephalomyelia. A study of Weed's[23] reproductions of pig embryos, shows that this distention of the neural tube reaches its most advanced stage shortly after the appearance of the choroid plexus *(Fig. 9).* It then subsequently diminishes, i.e., the hydrocephalomyelia becomes compensated as the rhombic roof and the subarachnoid space become more permeable. The opening of the foramens of the fourth ventricle in fetal life permits, for the first time, perfectly free communication between the ventricles and the subarachnoid space.

The beating of the choroid plexus, which is a relatively enormous structure in the embryo *(Fig. 10),*[24] acts as an unvalved pump to generate a pulse wave in the ventricular fluid.[25] This ventricular fluid pulse wave, funneled into the central canal in embryonal life, is shunted into the subarachnoid space after the foramens of the fourth ventricle open. The bypassed central canal, then com-

Fig. 9. An 18-mm. and a 26-mm. pig embryo with the cerebrospinal fluid spaces outlined by precipitated crystals of Prussian blue. In the 18-mm. embryo the ventricular fluid is just beginning to push through the permeable rhombic roof (arrow). In the 26-mm. embryo, as a result of dissection by the extruded fluid, the subarachnoid spaces have expanded to their adult configuration (L. H. Weed[23]). While the crown-rump length and the anteroposterior diameter of the embryo have increased less than 50 per cent, the lumen of the neural tube by comparison has enlarged tremendously. Hydrocephalomyelia, therefore, is a normal state in embryonal development. (Courtesy of The Carnegie Institution of Washington: Weed, L. H.: Contributions to Embryology, Vol. V, No. 14, Inst. Pub. No. 225, 1917, 116 pp.)

pressed from without and containing no choroid plexus, subsequently narrows to become a vestigial structure *(Fig. 11, A and B)*. The central canal may enlarge in postnatal life if the foramens of the fourth ventricle become occluded so that ventricular fluid once more can distend it. This is shown by the development of hydrocephalus, hydromyelia, and syringomyelia when the foramens are sealed experimentally by reaction to the intracisternal injection of kaolin[26] *(Fig. 12)*.

It was Chiari's belief that the deformity of the hindbrain which he described is the result of hydrocephalus of the forebrain. Weed[23] has pointed out that should the rhombic roof not be adequately permeable in embryonic life, obstructive hydrocephalus will ensue which in turn may result in communicating

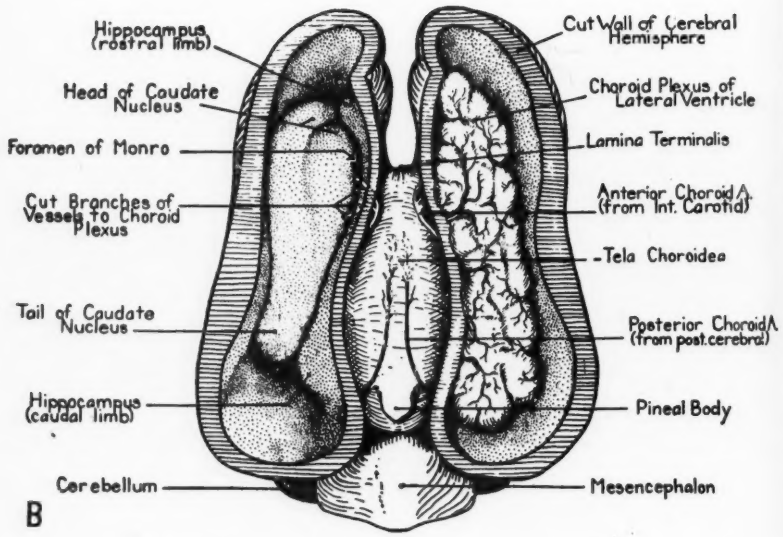


Fig. 10. The relatively enormous size of the choroid plexus and of the lateral ventricle is well shown in this diagram of the brain of a three-month human fetus cut horizontally. (Courtesy of Patten, B. M.: *Human Embryology;* modified after His; McGraw-Hill Book Company, Inc., 1946, 776 pp.)

hydrocephalus. Since in postnatal life hydrocephalus due to obstruction of the fourth ventricle results in a herniation of the hindbrain through the foramen magnum, the same thing may be anticipated in prenatal life—indeed more readily, since the immature dentate ligaments offer little resistance to the caudal dislocation of the hindbrain.*

In obstructive embryonal hydrocephalus, the central canal of the cord takes part in the dilatation. This cavity, normally a slit, is thus converted into a distended cylindrical tube that displaces and distorts the sclerotomes on each side of it *(Fig. 13).* A distorted sclerotome can scarcely be expected to develop into a normal bone. A pair of sclerotomes separated from each other by a distended neural tube may fail to unite, resulting in bilateral hemivertebra.

**The reason why the fourth ventricle is compressed in the Arnold-Chiari malformation and dilated in the Dandy-Walker malformation will be dealt with in a subsequent communication.*

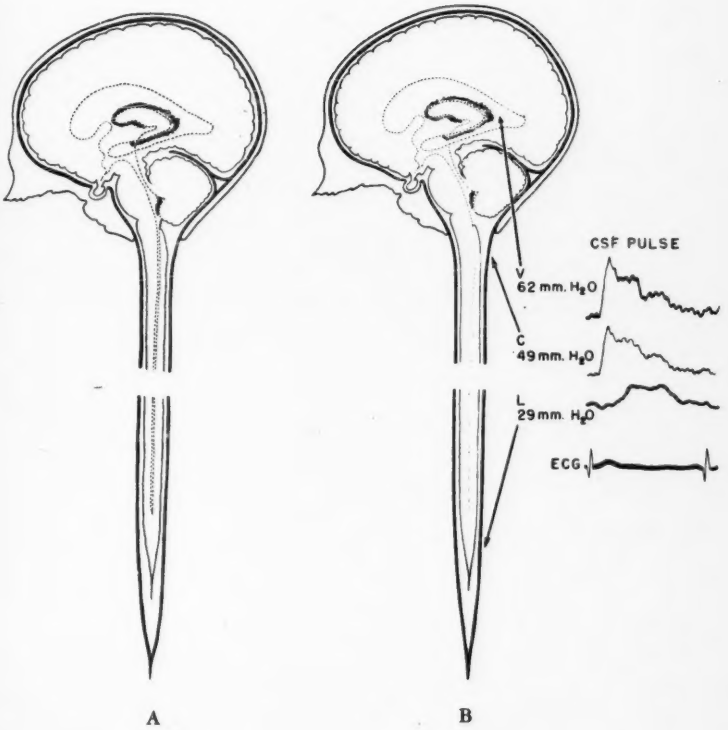


Fig. 11. A, Prior to the opening of the foramens of the fourth ventricle, the central canal of the cord, distended by ventricular fluid, constitutes an offshoot of the ventricular system. B, After the foramens open, the pulse wave of the ventricular fluid is shunted into the expansible spinal subarachnoid space on the outer surface of the cord and the central canal gradually narrows. The figures indicating the height of the pulse waves at various levels are from Bering.[25]

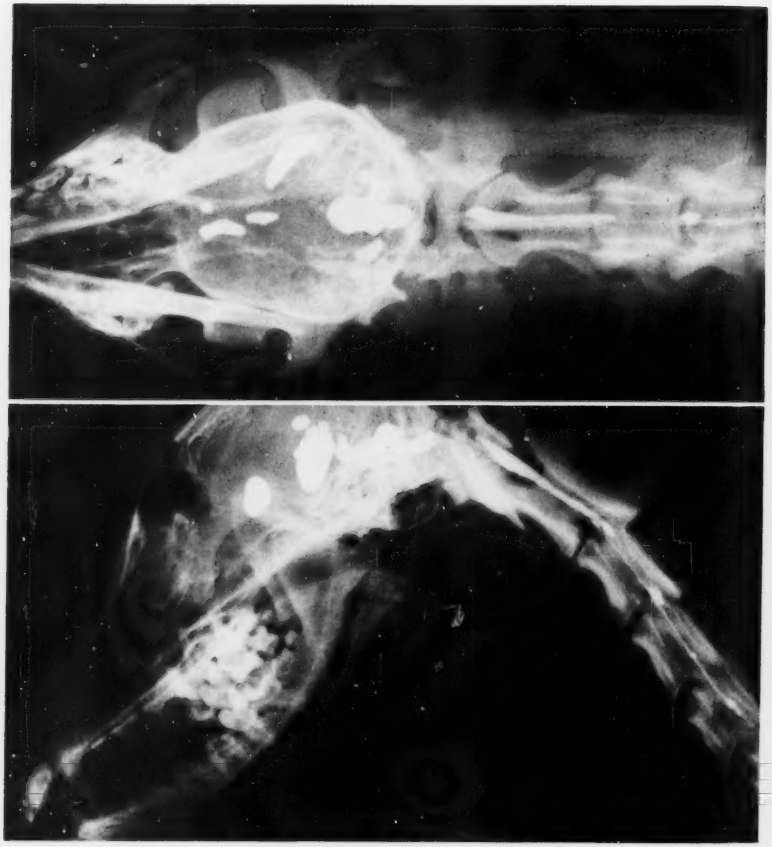


Fig. 12. In experimental hydrocephalus, injection of Pantopaque into the obstructed fourth ventricle shows that it communicates with the dilated central canal. This represents acquired hydrocephalomyelia. (Courtesy of McLaurin, R. L.; Bailey, O. T.; Schurr, P. H., and Ingraham, F. D.: A.M.A. Arch. Path. 57: 138-146, Feb. 1954.)

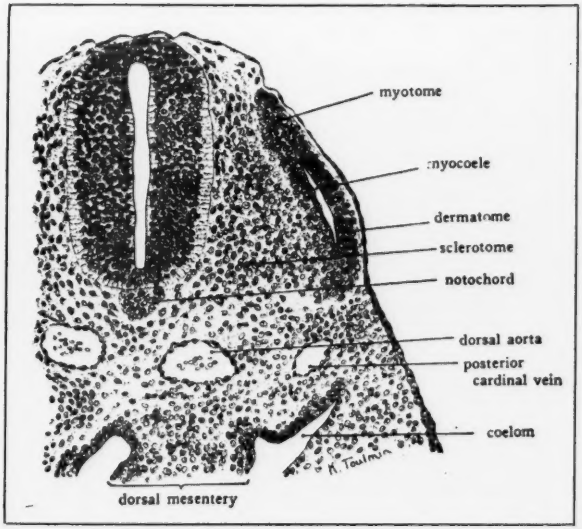


Fig. 13. Drawing from a transverse section of a 30-somite pig embryo. Note the slitlike neural tube bordered on each side by the skeletal anlagen. (Courtesy of Patten, B. M.:*Human Embryology;* modified after His; McGraw-Hill Book Company, Inc., 1946. 776 pp.)

Summary

The several anatomic anomalies, shared by the infant with myelomeningocele and the adult with syringomyelia, support the belief of earlier writers that there is a relationship between these states.

Hydrocephalomyelia is present in the embryo prior to the opening of the foramens of the fourth ventricle. In postnatal life it is found in cases where these foramens have failed to open adequately, as in the infant with myelomeningocele, and in the adult with syringomyelia. This suggests that in the latter conditions, the embryonal state of hydrocephalomyelia has been preserved by the inadequate permeability of the foramens of the fourth ventricle; that a normal individual results when embryonal hydrocephalomyelia becomes compensated at the normal time; that syringomyelia results when it becomes compensated too late; that myelomeningocele results when it does not become compensated at all.

This hydrodynamic theory will explain not only the anomalies of the central nervous system common to these states but the anomalies of the skeleton as well.

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A SELF-CALIBRATING BLOOD-PRESSURE MONITORING SYSTEM

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MONITORING during surgical procedures has become standard practice, particularly during operations on the heart and the vascular system. Initially, the electrocardiogram alone was monitored; it gave useful information relative to the development of arrhythmias but few other data of clinical value. Monitoring the electroencephalogram may be helpful in determining at any particular moment the level of anesthesia and the adequacy of cerebral blood flow.

A notable decrease in arterial blood pressure may occur during anesthesia, without the development of clinical signs of hypotension or abnormality in the electrocardiogram or in the electroencephalogram. Although the anesthesiologist periodically records the arterial pressure indirectly, a continuous record is highly advantageous because changes in pressure may be sudden and critical. Under some circumstances, induced hypotension may be utilized to facilitate surgical procedures; during the hypotensive phase the arterial blood pressure may be difficult or impossible to determine by the indirect method. Strain gauges and other transducers have been used to record the arterial pressure directly. The level of pressure must be determined by reference to a calibration, and recording must be done on paper. This method of recording requires the presence of trained personnel. A need for a method of recording the arterial blood pressure continuously and displaying it instantaneously without reference to previous calibration has become apparent. It should be possible to display the record on the screen of a cathode-ray oscillograph.

We are reporting the development of a measuring and monitoring system in which a number of pressures are sequentially sampled by valving these pressures to a common chamber that is covered by a diaphragm coupled mechanically to a simple linear transducer *(Fig. 1)*. The blood pressure and calibration information are reproduced on a cathode-ray tube or on a suitable paper recorder.

In its simplest form, three pressures are used. Two of these are accurately known static pressures that are continuously adjustable and measurable by means of mercury manometers. The third is the direct arterial pressure communicated to the valve-transducer system by means of a nylon tube or catheter. By sequentially sampling the accurately known pressures and the arterial blood pressure, the system is continuously calibrating itself ten times per second at two pressure levels *(Fig. 2)*. The arterial pressure is effectively superimposed on these calibration points, permitting accurate measurement or observation of the complete arterial pressure curve and measurement of systolic and diastolic pressures. Venous pressure also may be measured by this method.

The basic element of the pressure scanner is the stainless-steel, high-precision,

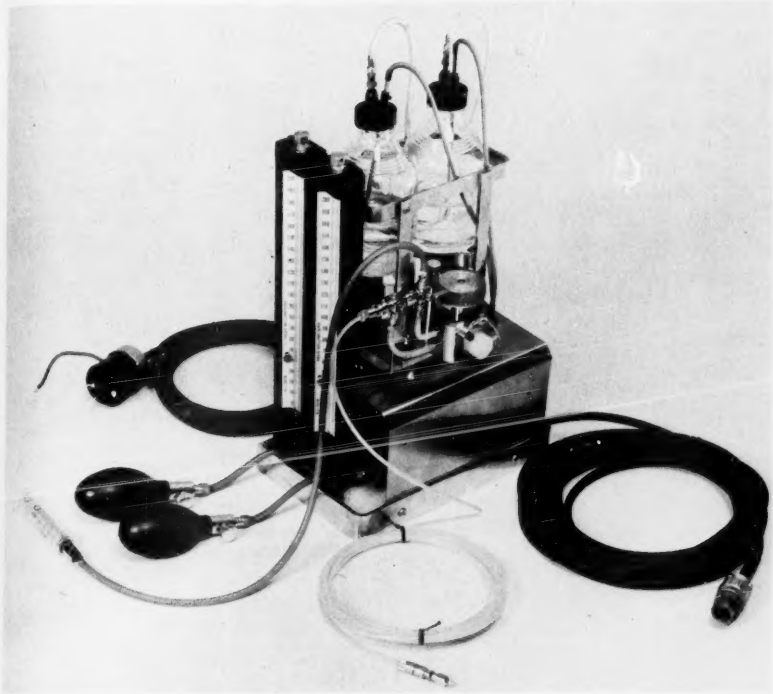

Fig. 1. Photograph of blood-pressure monitoring equipment.

all-metal, motor-driven valve that opens in sequence between the transducer pressure chamber and four pressure sources *(Figs. 3 and 4)*. The timing is so arranged that the previously sampled pressure is completely turned off an instant before the succeeding pressure to be sampled is turned on. Each sampling of pressure in its proper turn therefore actuates the ceramic piezoelectric transducer. The transducer chamber with its heavy, stainless-steel diaphragm is bolted directly to the valve body, forming a gasketless seal between precision-honed metal surfaces. The transducer element is cemented directly to the diaphragm. This element is lead zirconium titanate (PZT), a high-sensitivity piezoelectric ceramic material that is unaffected by temperatures up to 300 C.

The necessary operations of filling the valve and tubing with sterile liquid and of removing air are performed with the aid of three, standard, four-way stopcocks. The static calibrating pressures and a standard syringe provide the means of forcing the sterile liquid through any part of the system selected by the positions of the stopcocks. All air is released from the valve through the air-release

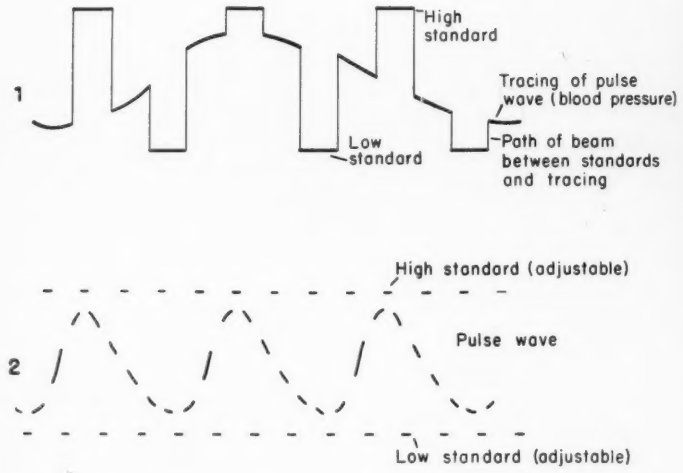

Fig. 2. Diagram of transducer output. The straight lines represent static pressures, and the curved lines represent intravascular pressures.

port, which is capped by a standard Luer slip plug. The static-pressure ports are each kept open one fourth of a valve revolution *(Fig. 5)*. In the simplest form, this allows one half of a revolution in which the arterial pressure is in communication with the transducer.

Since actuation of the transducer depends on deflecting a small, extremely stiff, stainless-steel diaphragm one-eighth inch in thickness, the frequency response depends entirely on the size of the inside diameters and the expansion rigidity of the catheter system. In actual operation, as the scanning valves open and close, the pressure in the transducer chamber is changed and precisely measured in less than one thousandth of a second, forty such changes occurring each second. These pressure changes and measurements take place entirely independently of the external catheter system and represent a maximum attainable frequency response of several thousand cycles per second.

This system eliminates the need for direct-current amplifiers and centering controls. The read-out automatically returns to center on the cathode-ray screen. It is independent of transducer or amplifier calibration, and does not require extremely high-gain amplifiers. The system is simple to operate. It can be sterilized by autoclaving or with chemicals.

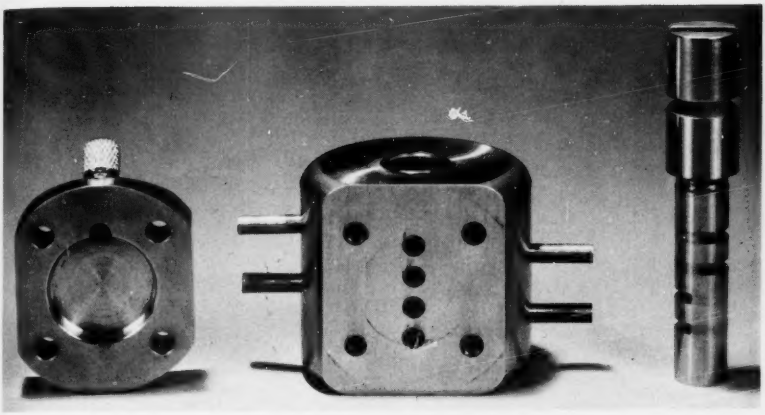

Fig. 3. Photograph of valve.

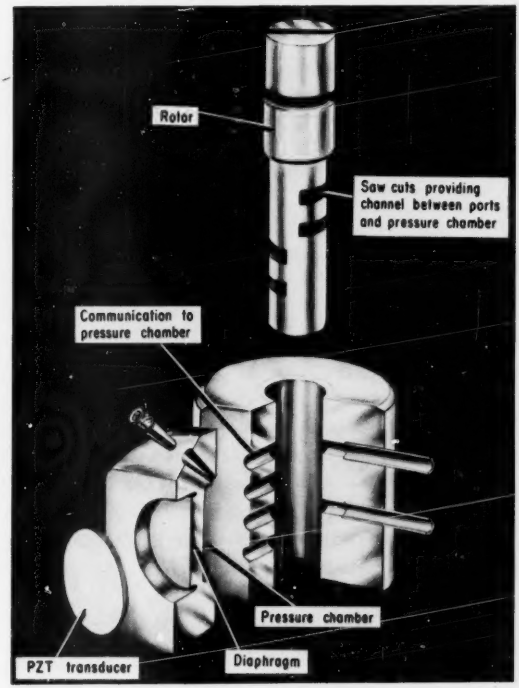

Fig. 4. Diagram of valve.

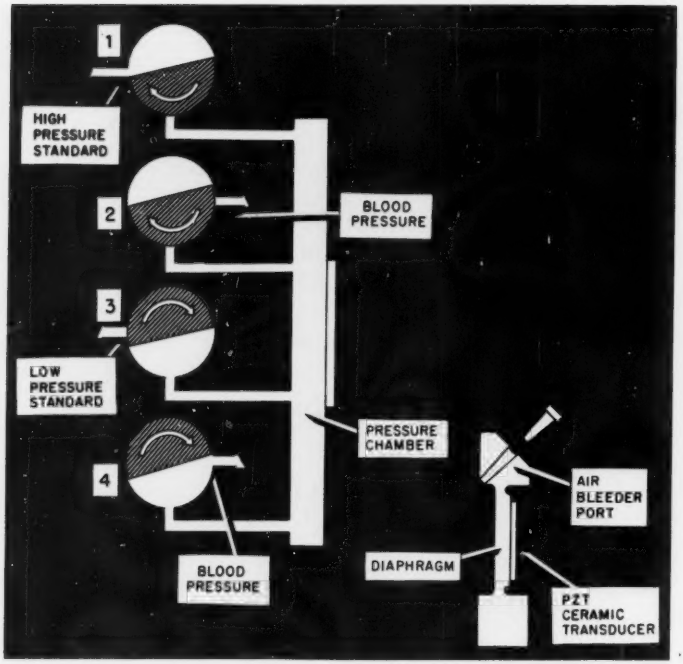

Fig. 5. Diagram of transducer. The circles represent cross sections of the stator, showing: 1—high pressure standard closed, to open in one-half turn; 2—blood pressure closed, to open in one-quarter turn; 3—low pressure standard, about to register; 4—blood pressure registering at end of dwell.

To facilitate autoclaving, to avoid special parts, and to provide hydraulic shock absorption, standard latex heavy-wall rubber tubing is used to connect the system of standard stopcocks to the scanning valve. With this unsupported rubber tubing, reliable frequency response of more than 10 cycles per second is available with a catheter consisting of six feet of nylon tubing, with a 0.078-inch inside diameter, terminating in a No. 18 needle. This response is adequate for accurately recording the arterial blood pressure.[1] With a larger diameter and more rigid catheter system, much higher frequencies can be obtained.

The noise level of the complete scanner system is less than the equivalent of a pressure at 1 mm. of Hg. Therefore, pressures of less than 10 mm. of Hg can be satisfactorily monitored and measured.

An excellent paper record of the pressures can be made with any photographic recorder having a frequency response of 300 cycles per second or more *(Fig. 6)*. Most of the standard direct-writer recorders will also produce an accurate and satisfactory record. A recording can also be made by removing the green or amber

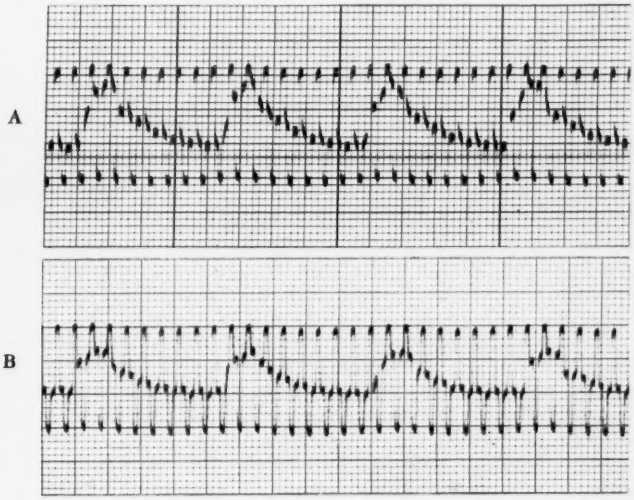

Fig. 6. Human arterial blood-pressure curves. A, Photographic record (Sanborn Model 62). B, Direct writer record.

filter of an oscilloscope and photographing the screen with an ordinary camera by holding the camera open for the duration of one sweep.

Summary

A new transducer system for recording the direct arterial blood pressure has been developed, by means of which it is possible to display continuously known pressures and the arterial pulse curve on the screen of a cathode-ray oscilloscope, and to record the curves by means of a suitable galvanometer.

Acknowledgment

We are indebted to Mr. John Cox, President of the Balas Collet Company, for construction of the valve, and to Mr. Carmen Germano and Dr. Donald Faulk of the Clevite Corporation for advice relative to the transducer element and for furnishing the piezoelectric material.

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ENDOTRACHEAL ANESTHESIA USING A MODIFIED WIS-FOREGGER LARYNGOSCOPE BLADE

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Department of Anesthesiology

ENDOTRACHEAL intubation is widely employed during general anesthesia. This technic provides definite advantages to the patient, the surgeon, and the anesthetist. However, skillful use of the laryngoscope is essential to avoid injury to the patient's teeth and pharynx during intubation. Although such injuries are accepted hazards of the procedure, they may be avoided by the use of a laryngoscope with a modified blade.

Technic of Laryngoscopy

Laryngoscopy for intubation must be done with gentleness and precision. While the standard laryngoscopic procedure is modified and individualized by each anesthetist, the fundamental principles of the technic remain unchanged. The patient's head is held in progression by elevating it from the pillow. Such manipulation relaxes the anterior muscles of the neck, and straightens the normal anatomic curves of the pharynx. The blade of the laryngoscope is lifted upward and forward[1] to carry forward the epiglottis and the base of the tongue to expose the larynx and the vocal cords. The endotracheal tube then can be easily inserted into the trachea under direct vision.[2] Should the laryngoscope be used as a lever, with the upper incisor teeth acting as the fulcrum, there is risk of damaging the teeth and of traumatizing the epiglottis.[3]

Difficult Intubations

Anatomic variations of the mouth and the pharynx occur frequently. Many of them are the cause of difficulty in exposing the larynx and in intubating the trachea. The problem is exemplified in patients who have any of the following features: a small mouth, a short thick neck, an anteriorly placed trachea, a short thick epiglottis, a recessed mandible, a "frozen" temporomandibular joint, protruding upper incisor teeth. In these patients, difficult intubation is common, and the unfortunate traumatizing of the pharynx or damaging of the teeth is apt to occur. The anesthetist should be forewarned that disfigurement from damaged teeth may well provoke litigation against him by the patient.

Modification of the Wis-Foregger Blade

The regular blade of the Wis-Foregger laryngoscope* (infant, child, adult, long sized blades) is detachable, and forms a right angle with the Foregger handle. *Figures 1* and *2* illustrate the differences between the regular and the modified Wis-

**Manufactured by The Foregger Company, Inc., 55 West 42 Street, New York, New York.*

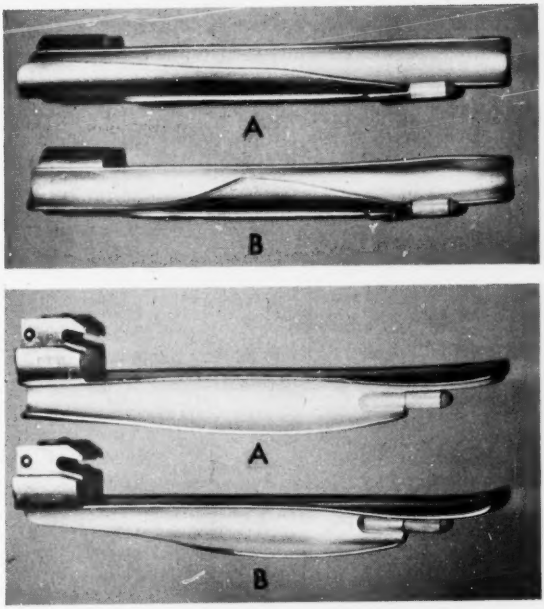

Fig. 1. Photographs of A, the regular, and B, the modified Wis-Foregger laryngoscope blades (top and side views).

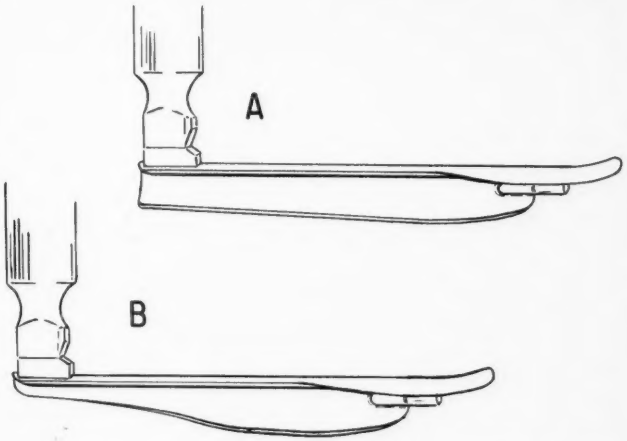

Fig. 2. Sketches of A, the regular Wis-Foregger laryngoscope blade, and B, the modified blade with tapered contour (side view).

consin blades. In the modified blade, the inferior surface of the blade has been cut away to a distance of 7 cm. while maintaining a gradual taper. Removal of that portion of the blade does not jeopardize the strength of the instrument.

The clinical advantages of the modified blade are apparent. For visualization of the larynx, the blade requires an upward and forward lifting force; therefore, the handle of the laryngoscope does not become a lever nor do the teeth act as the fulcrum for the blade in exposing the larynx. Should the blade be permitted to rest on the teeth, visualization immediately becomes impossible *(Fig. 3)*.

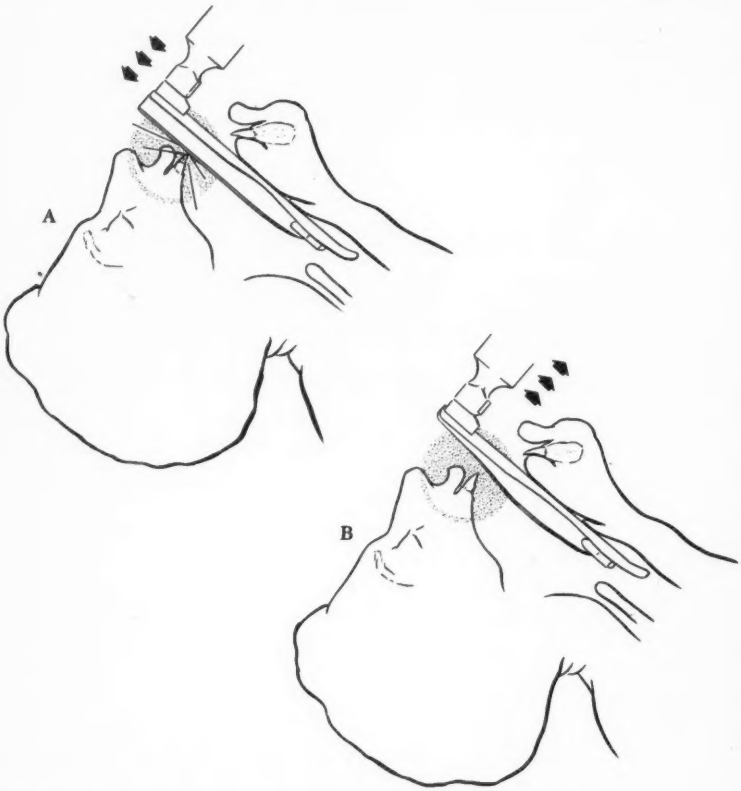

Fig. 3. Sketches showing technics using A, the regular Wis-Foregger laryngoscope blade, and B, the modified blade.

Trauma to the undersurface (posterior) of the epiglottis is minimized by applying the proper lifting force. Moreover, the alteration in design of the blade reduces

the amount of bulk put into the mouth of the patient, thus providing better visibility.

Legal Aspects of Injury to the Teeth

As mentioned previously, injury to the teeth during laryngoscopy for endotracheal intubation is not uncommon. Frequently, a difficult intubation cannot be anticipated; permanent dentures may complicate the technic. The anesthetist should do everything possible to avoid such injury, and the modification of his equipment is a simple but effective step in this direction.

As a general rule, it may be stated that the law recognizes the possibility of complications, and places the risk of their occurrence upon the patient, so long as there is no negligence on the part of the anesthetist. By such a premise, the anesthetist does not have license to extract teeth needlessly during intubation. Despite this legal immunity, it behooves the anesthetist to protect the patient's teeth during intubation. This may be accomplished with the rubber tooth protector,[4] and by modifying the potentially dangerous parts of existing equipment. These precautions constitute the exercise of reasonable care.[5]

Conclusions

The modification of the blade of the Wis-Foregger laryngoscope facilitates intubation by averting trauma to the patient's teeth, the dental prostheses, and the epiglottis. When used incorrectly—as a lever, with the teeth as the fulcrum—the modified laryngoscope blade obscures the anesthetist's view of the larynx, and intubation under direct vision becomes impossible. Therefore, the only manner in which the instrument can possibly be used to intubate a patient is the correct, nonnegligent way.

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REMISSION OF LESIONS IN MYCOSIS FUNGOIDES FOLLOWING TOPICAL APPLICATION OF NITROGEN MUSTARD

A Case Report

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and
DOUGLAS J. GRANT, M.D.†
Department of Dermatology

METHYL-BIS-(β-CHLOROETHYL) AMINE HYDROCHLORIDE, commonly known as nitrogen mustard, is a nitrogen analogue of sulfur mustard, the vesicant gas of World War I. In 1931, Adair and Bagg reported that the topical and intralesional use of sulfur mustard in the treatment of numerous types of primary and secondary cutaneous malignant lesions gave good initial results, but this therapeutic moiety was subsequently neglected.

Following the development of nitrogen mustard, investigational studies[2] into its actions led to the recognition of the similarity of these actions to those of irradiation. Shortly afterwards, nitrogen mustard was used intravenously in the treatment of various forms of lymphoma.[3-5] Its use then became extended to the local treatment of malignant effusions in the pleural and peritoneal cavities, and in rheumatoid arthritis[6] to the intraarticular cavities.

The purpose of this preliminary report is to present a case of remission in lesions of mycosis fungoides after the local applications of diluted nitrogen mustard solution. To our knowledge this is the first such observation.

Report of a Case

In 1956, a 28-year-old white man was examined by his local physician because of a blotchy nonpruritic axillary eruption. The diagnosis of mycosis fungoides was confirmed by biopsy. Twelve applications of roentgen therapy were given but brought no relief, and the patient was then referred to the Cleveland Clinic.

At the time of our initial examination in February, 1958, the eruption showed discrete, nummular, pea to silver dollar sized erythematous scaling, slightly infiltrated lesions predominantly in the groin and in the axillae. The other findings from the physical examination were essentially normal, and laboratory studies were noncontributory.

During the next thirteen months the lesions became more numerous and widespread, heavily infiltrated, nodular, and pruritic. On April 4, 1959, the patient was admitted to our hospital for treatment. Nitrogen mustard was administered intravenously on three alternate days for a total dosage of 0.4 mg. per kilogram of body weight. During this course of therapy, on three successive days nitrogen mustard was applied topically to half the area of each of two placques on the patient's arms. Several days later, pruritus

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had disappeared, the lesions began to regress, and the patient was discharged from the hospital. Within three weeks there was recurrence *(Fig. 1)* in all lesions except in the sites treated topically with nitrogen mustard.

Fig. 1. Lesions of mycosis fungoides before topical therapy.

Fig. 2. Lesions of mycosis fungoides three weeks after topical therapy with nitrogen mustard solution.

The patient was readmitted to the hospital on June 24, 1959, for further topical therapy. Most of the recurrent lesions were covered with gauze pads that were dampened with a solution of nitrogen mustard (10 mg. per 50 ml. of saline solution). The pads were left in place for 15 minutes. This treatment was applied on three consecutive days. Within 48 hours of the last application the lesions became mildly erythematous and then gradually flatter, nonpruritic, and less infiltrated *(Fig. 2)*. Lesions that were not treated showed no regression. There was no evidence of systemic toxicity; there were no changes in the hemoglobin content and in the leukocyte count; and there was no reactivation of lesions during the month following treatment.

Discussion

The complications of nitrogen mustard intravenously administered are well known. Toxic systemic reactions occur, such as nausea, vomiting, and depression of formed elements in the circulating blood. This toxicity limits the size of the individual dose of nitrogen mustard and the frequency of its administration. It appears from our preliminary studies that these reactions were avoided by topical application.

Nitrogen mustard in polar solvents, by intramolecular cyclization, forms highly reactive transient groups that are rapidly destroyed by self-interaction and contact with tissue elements. The effect exerted upon living cells by nitrogen mustard is intimately related to the mitotic activity of these cells; therefore, anaplastic tissues are more profoundly influenced than are well-differentiated tissues. Since nitrogen mustard is rapidly deactivated by tissue contact, little systemic effect would be expected from topical application. Consideration of the above factors led us to attempt the treatment of mycosis fungoides by the topical application of nitrogen mustard, despite the potential dangers of sensitization.[7]

Summary

A solution of nitrogen mustard, applied topically on three consecutive days to long-standing lesions of mycosis fungoides, gave good initial results and no evidence of sensitization or systemic toxicity. There was no reappearance of lesions topically treated during intravenous nitrogen mustard therapy, although the others did recur. Subsequent topical application has resulted in the regression of all lesions during the month of posttherapeutic observation.

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